Integration of Oncogenomics and Population Science to Improve Patient Outcome in Myeloma

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Multiple Myeloma

Plasmacytomas, bone marrow plasmacytosis, monoclonal protein

Median survival with conventional therapy 3-4 years, 4-5 years with high dose therapy and transplant, but remains incurable

Multiple Myeloma Epidemiology

14,400 new cases, 50,000 total cases, 2% cancer deaths in U.S.

High incidence in African Americans, Pacific Islanders

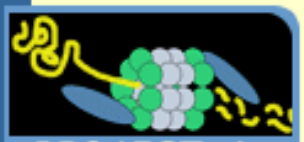
Mean age 62 yrs men, 61 yrs women

MGUS, irradiation or petroleum products, farmers, paper producers, furniture manufacturers, wood workers

Greenlee RT. CA Cancer Clin 2001;51:15
Bergsagel DE. Blood 1999;94:1174

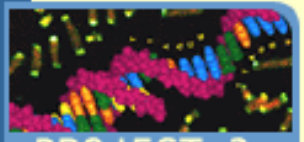
Specialized Program of Research Excellence in Myeloma

Dana Farber/Harvard Cancer Center



PROJECT 1

Proteasome-Directed Novel Myeloma Therapies
Kenneth C. Anderson - DFCI
Hidde Ploegh - HMS



PROJECT 2

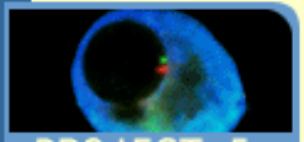
Targeting Telomere Expansion Mechanisms for Myeloma Therapy
Nikhil C. Munshi - DFCI
Ronald DePinho - DFCI

PROJECT 3

MUC1 as a Therapeutic Target in Multiple Myeloma
Donald Kufe - DFCI
J. Paul Eder - DFCI

PROJECT 4

Novel Therapeutics Targeting Genetic Abnormalities in Multiple Myeloma
Leif Bergsagel - Cornell
Paul Richardson - DFCI



PROJECT 5

Cytogenetic and Molecular Correlates of Evolution from MGUS to Multiple Myeloma
Rafael Fonseca - Mayo
Lynda Chin - DFCI

CORE 1 Administrative & Communication

CORE 2 Tissue

CORE 3 Functional Genomics & Bioinformatics

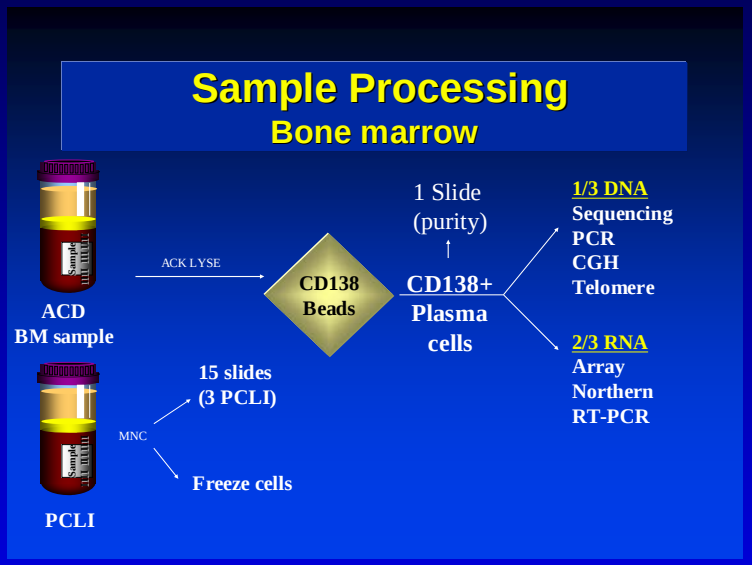
CORE 4 Biostatistics

Developmental Projects

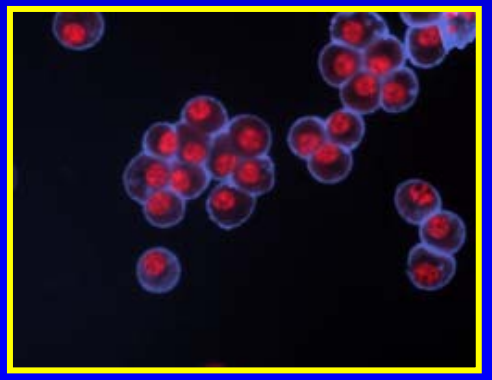
Associated Institutions

Intranet

Tissue Core



Pre-Selection



Post-Selection

Monoclonal Gammopathy of Unclear Significance

2% individuals > 50 years old

< 3.5 gm/L monoclonal Ig, little or no proteinuria

< 5% monoclonal BM plasma cells

No bone lesions, anemia, hypercalcemia or bone lesions

Kyle R. N Eng J Med 2002;346:564

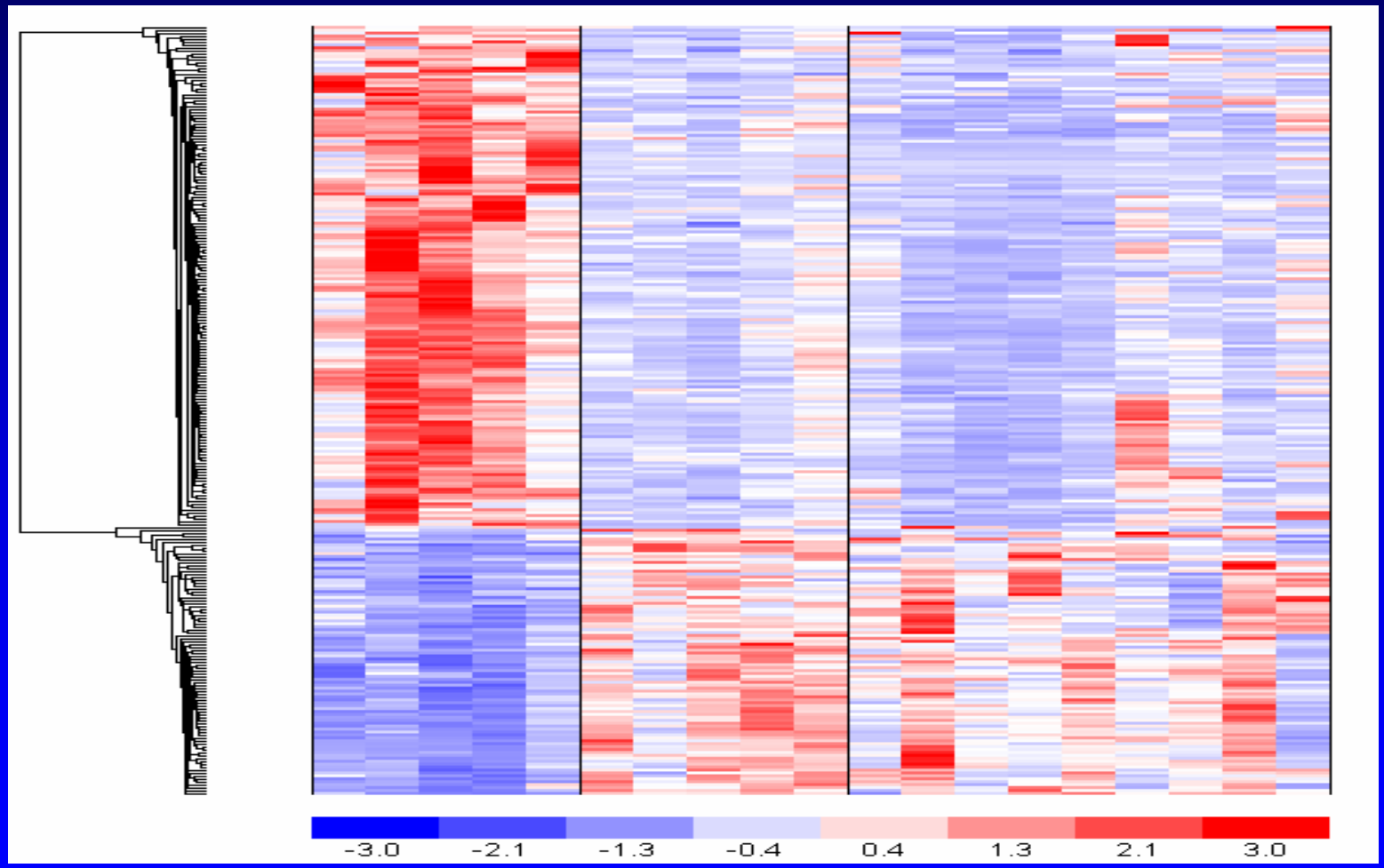
Monoclonal Gammopathy of Unclear Significance

Overall 1% progress each year, correlated with initial paraprotein level, to:

Disease	Relative risk
Multiple myeloma	25
IgM lymphoma	2.4
Primary amyloidosis	8.4
Macroglobulinemia	46
Chronic lymphocytic leukemia	0.9
Plasmacytoma	8.5

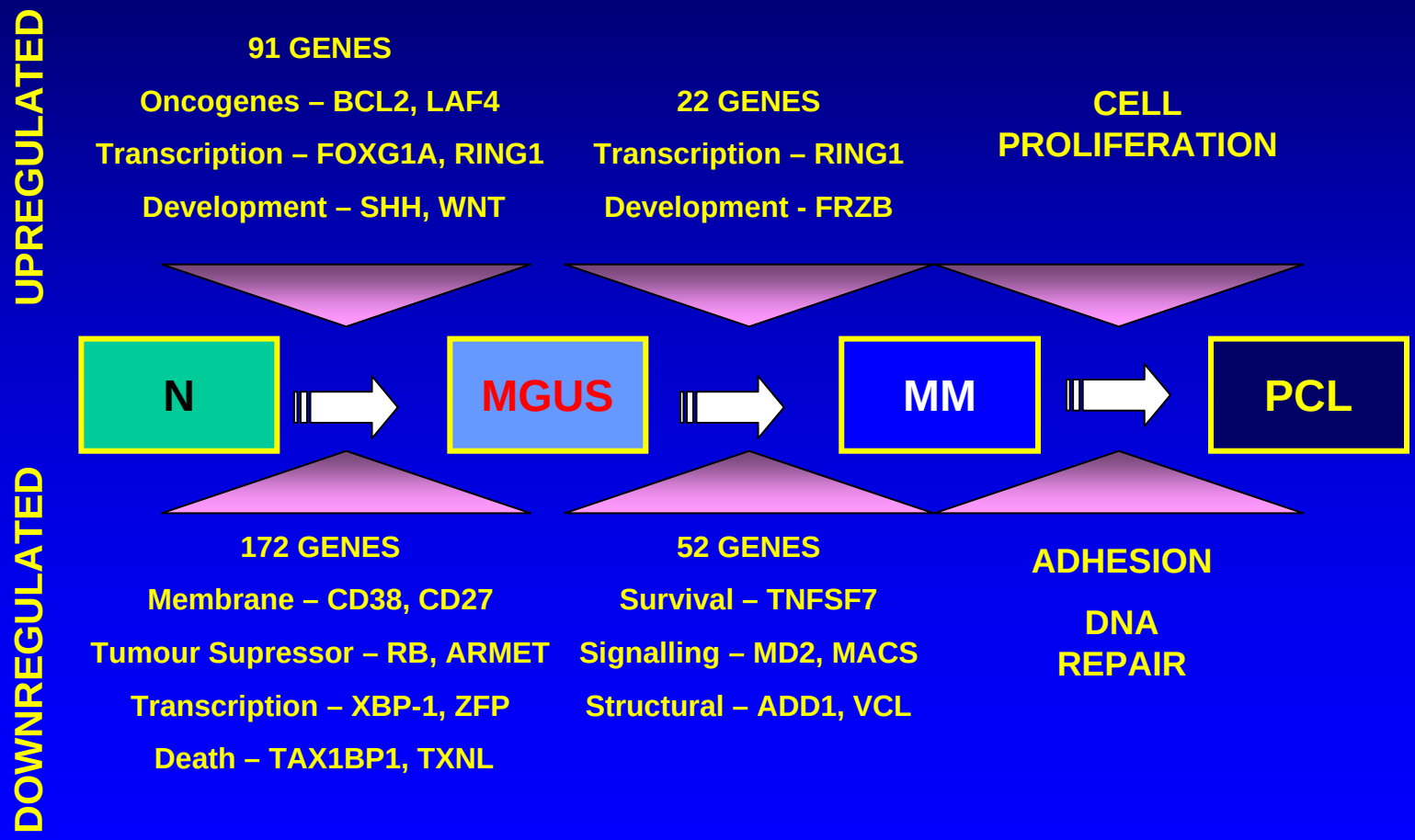
Kyle R. N Eng J Med 2002;346:564

Gene Expression Profiles Associated with Progression to Myeloma



Davies et al. Blood 2003;102:4504.

Molecular Pathogenesis of Myeloma

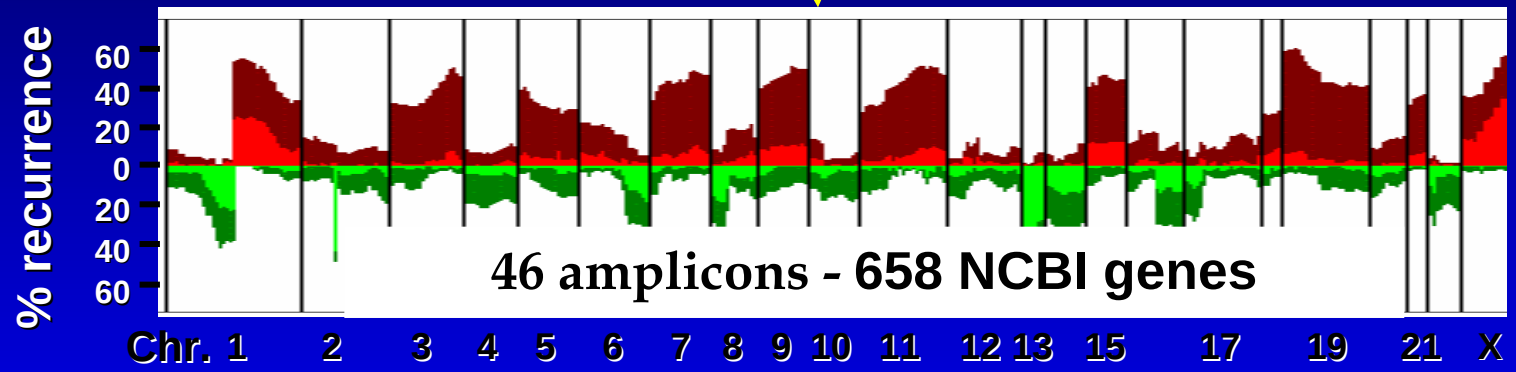


Davies et al. Blood 2003;102:4504.

Oncogenomics to Identify Targeted Therapies

Integrated platform aCGH, SKY and expression profiling

55 MM Cell Lines; 73 Patient Samples



Expressed Genes : **258**

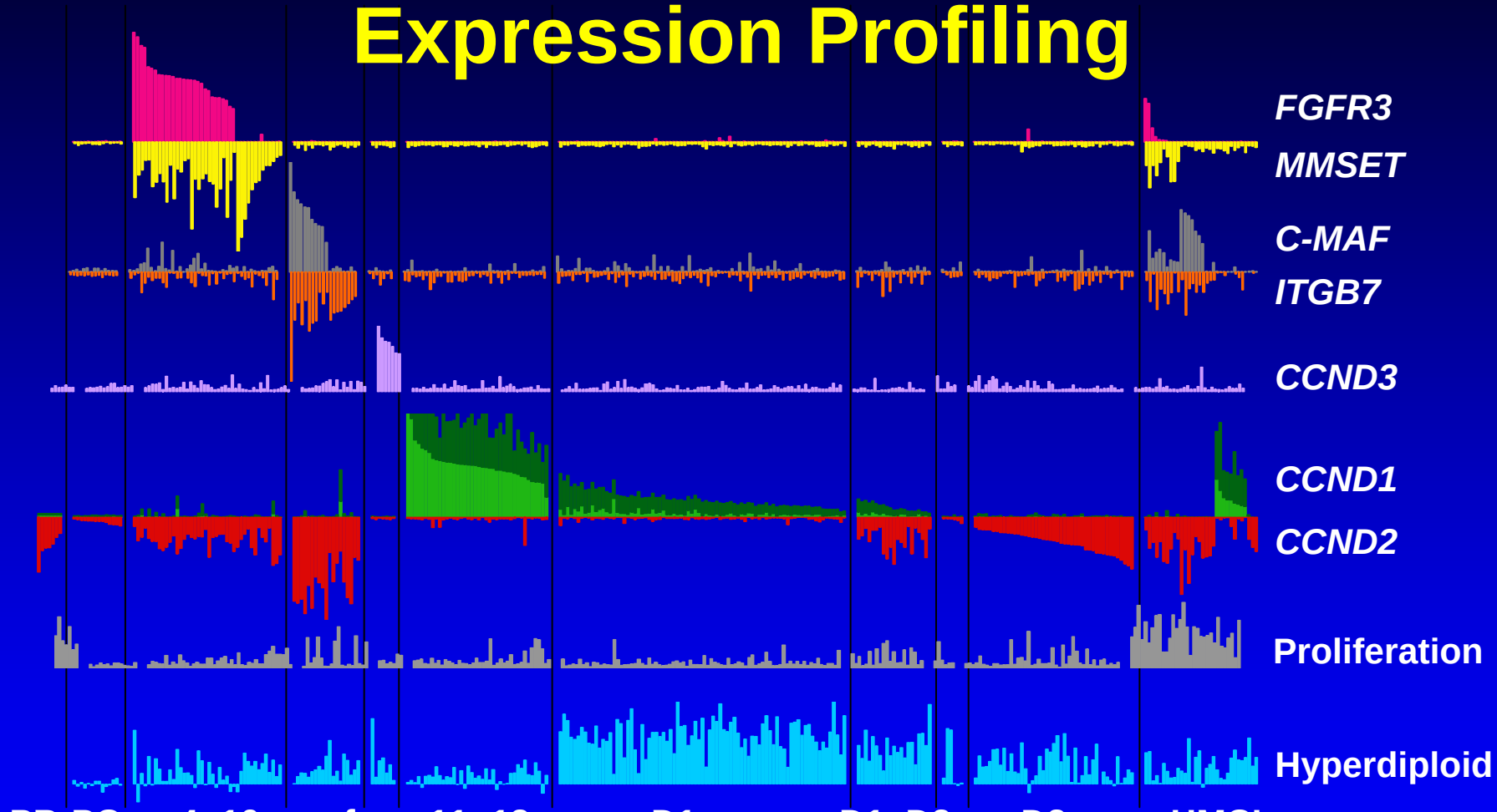
Functional validation of MM candidate genes.

Small molecule

Monoclonal Abs

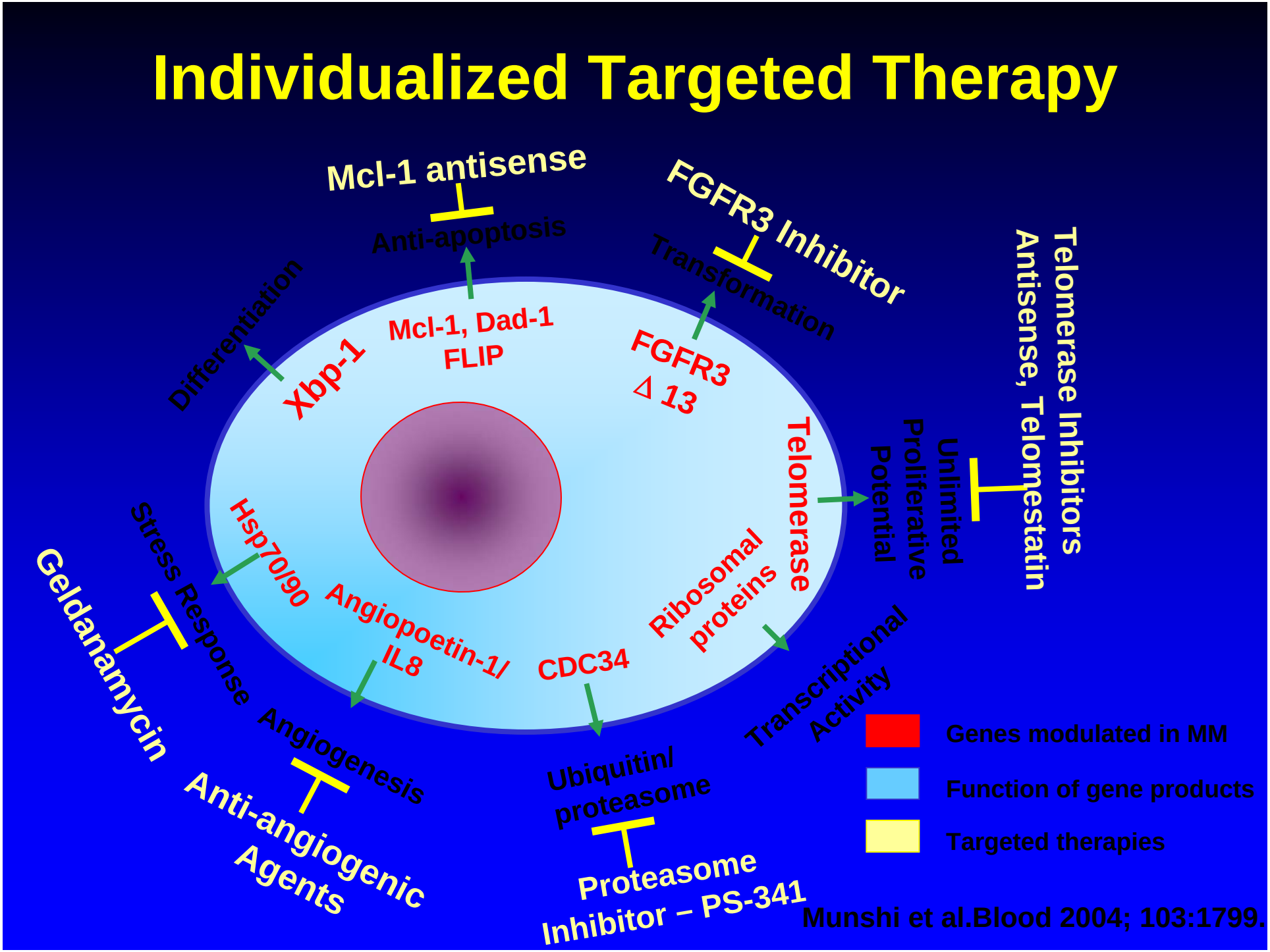
Anderson and Depinho

Classification Based upon Expression Profiling



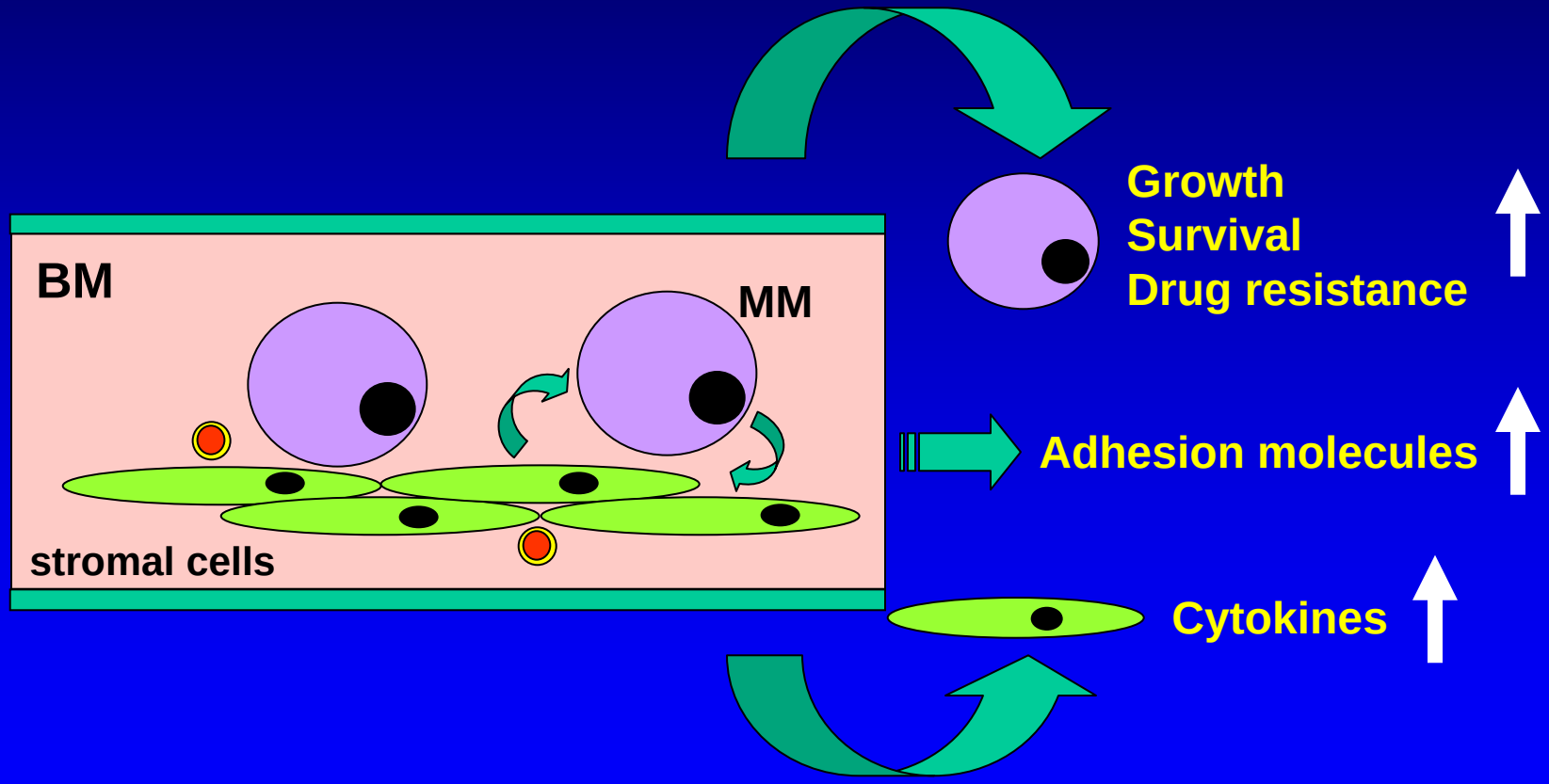
Bergsagel et al, Blood 2005

Individualized Targeted Therapy

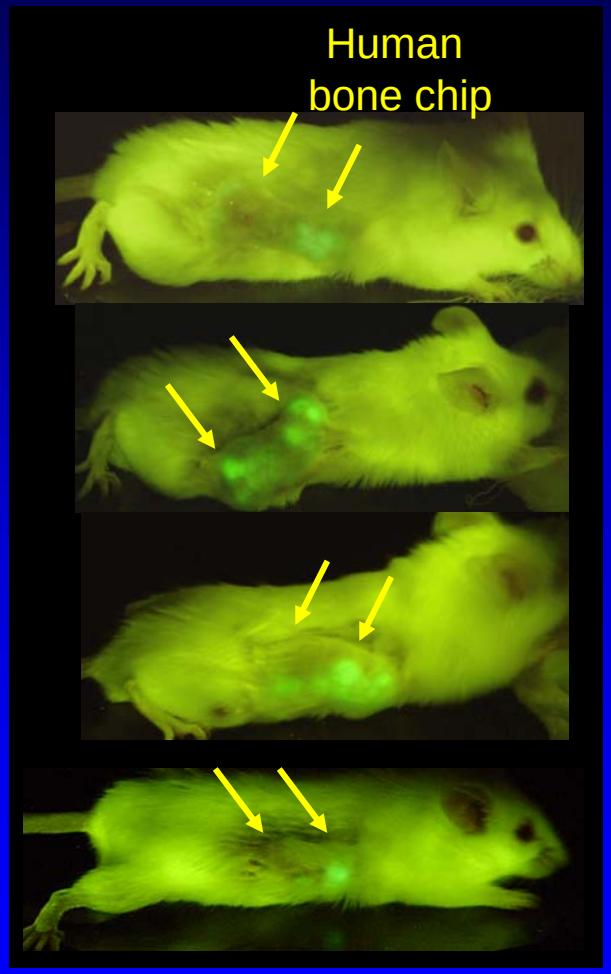


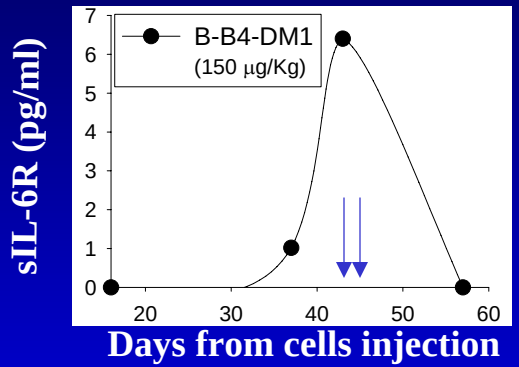
Munshi et al.Blood 2004; 103:1799.

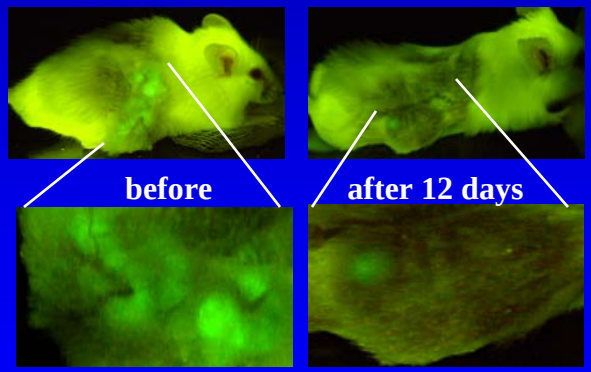
Gene Modulations Triggered by Binding of MM Cells to BMSCs



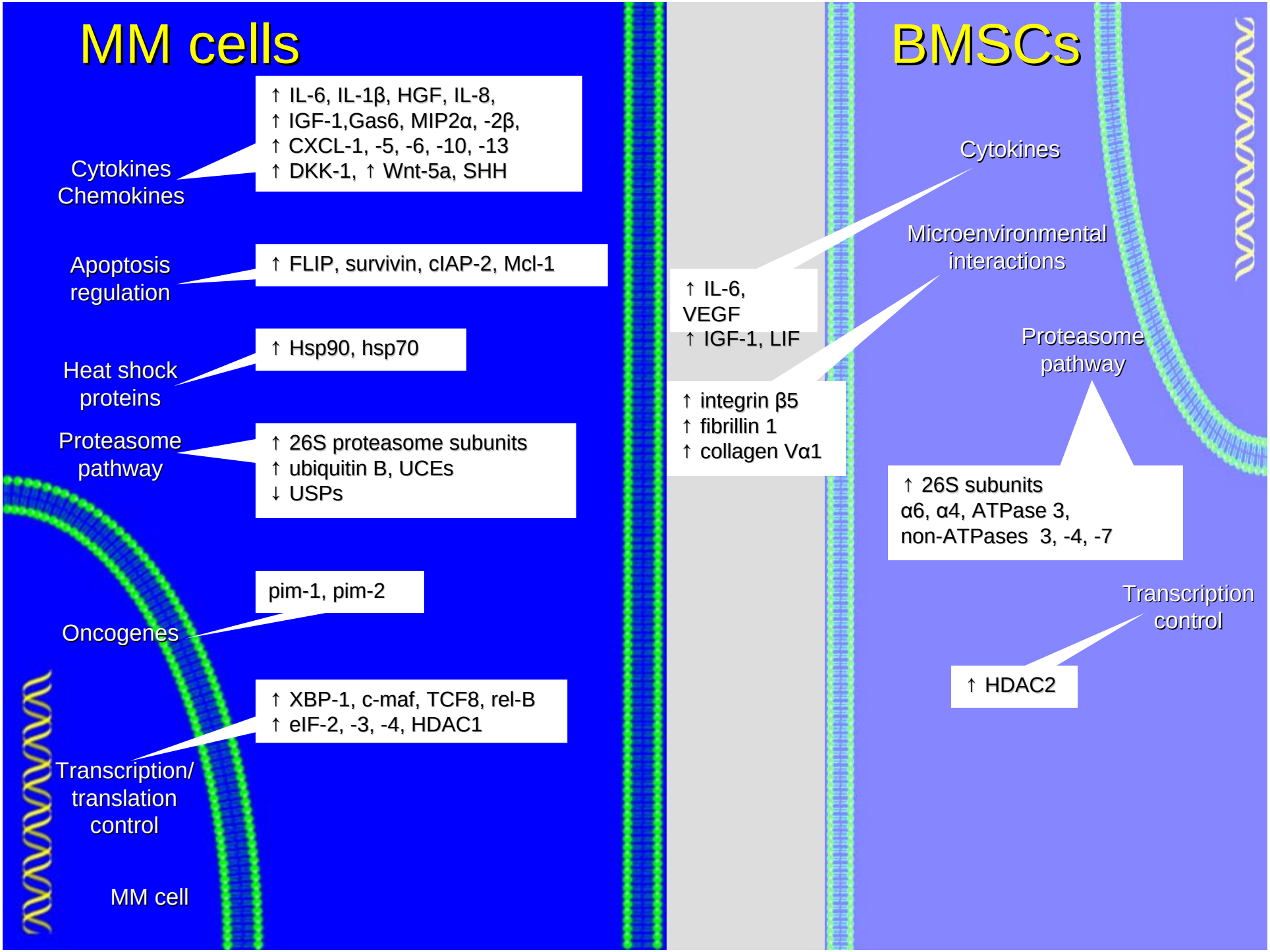
In vivo Model of Human MM in Human BM Milieu



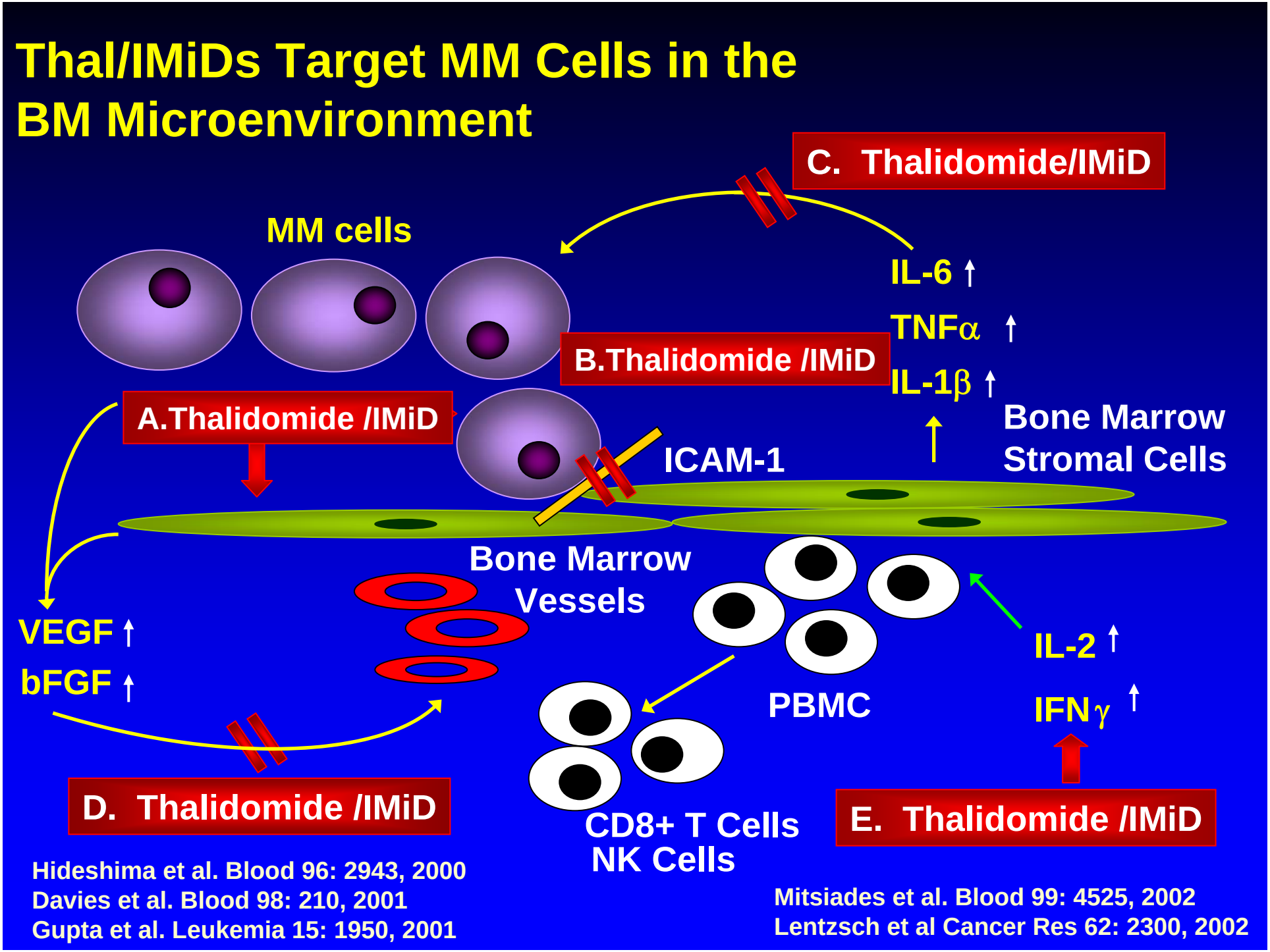




Tassone P. et al., Blood, 2005


MM cells
BMSCs
↑ IL-6, IL-1β, HGF, IL-8,
↑ IGF-1,Gas6, MIP2α, -2β,
↑ CXCL-1, -5, -6, -10, -13
↑ DKK-1, ↑ Wnt-5a, SHH
Cytokines
Chemokines
Apoptosis regulation
↑ FLIP, survivin, cIAP-2, Mcl-1
Heat shock proteins
↑ Hsp90, hsp70
Proteasome pathway
↑ 26S proteasome subunits
↑ ubiquitin B, UCEs
↓ USPs
pim-1, pim-2
Oncogenes
↑ XBP-1, c-maf, TCF8, rel-B
↑ eIF-2, -3, -4, HDAC1
Transcription/ translation control
MM cell
Cytokines
↑ IL-6,
VEGF
↑ IGF-1, LIF
Microenvironmental interactions
↑ integrin β5
↑ fibrillin 1
↑ collagen Vα1
Proteasome pathway
↑ 26S subunits
α6, α4, ATPase 3,
non-ATPases 3, -4, -7
Transcription control
↑ HDAC2

Thal/IMiDs Target MM Cells in the BM Microenvironment



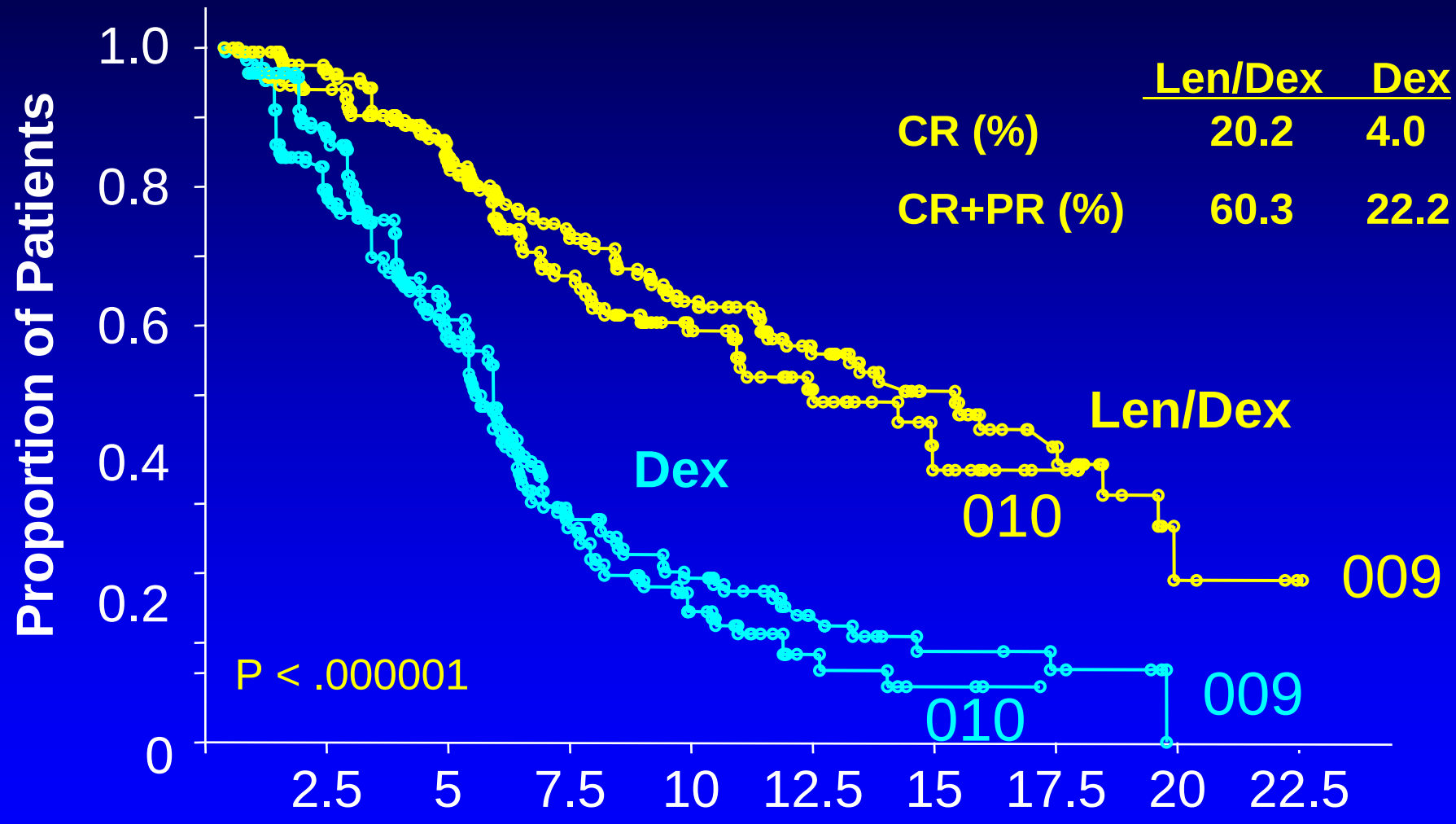
Hideshima et al. Blood 96: 2943, 2000
Davies et al. Blood 98: 210, 2001
Gupta et al. Leukemia 15: 1950, 2001

Mitsiades et al. Blood 99: 4525, 2002
Lentzsch et al Cancer Res 62: 2300, 2002

Bench to Bedside Development Of Revlimid Targeting MM Cell in its Microenvironment

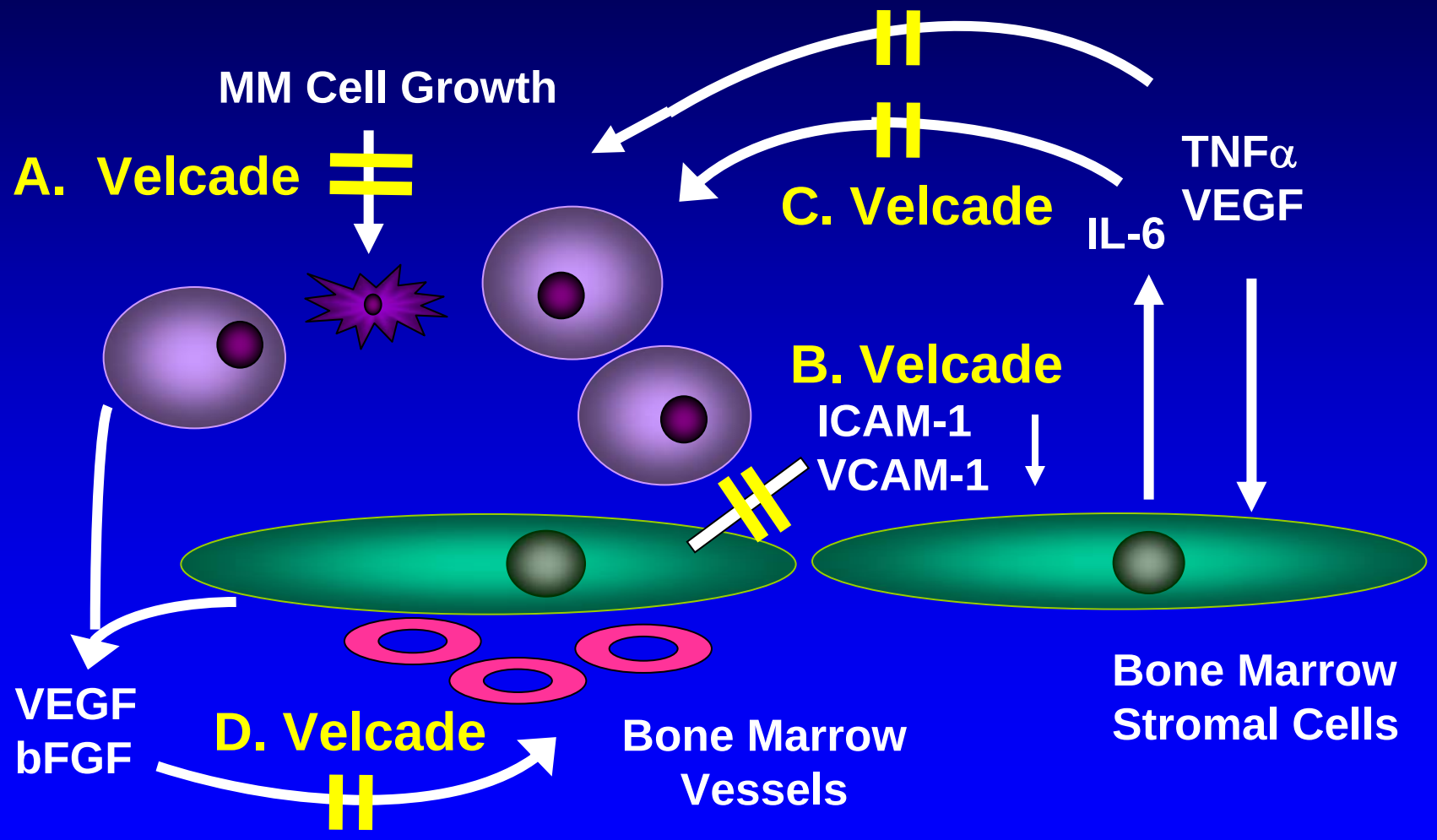
- Preclinical (2000): targets tumor (caspase-8 mediated apoptosis) and microenvironment in vitro and in vivo in animal model
- Phase I trial (2001): MTD; favorable toxicity; stable disease or response in 79% patients
- Phase II trials (2002-3): 80% stable disease or response
- Two Phase III trials (2003-4): Revlimid/Dex versus Dex/placebo in relapsed myeloma

Phase III Trials



	Len/Dex	Dex
CR (%)	20.2	4.0
CR+PR (%)	60.3	22.2

Velcade Targets MM Cells in the BM Microenvironment



Hideshima et al. Cancer Res 61: 3071, 2001
Hideshima et al. Oncogene 20: 4519, 2001

Mitsiades et al. Blood 99: 4079, 2002
Hideshima et al. J Biol Chem 277: 16639, 2002

Bortezomib: From Bench to Bedside

1994 NF-κB is a therapeutic target in myeloma

1995-7 Drug discovered (Julian Adams), NCI 60 cell line

1998 Phase I trials started

2000 Phase I trials:safe and has anti-MM activity

2000 Targets MM cell and BM microenvironment to overcome drug resistance in laboratory and animal studies

2001 Phase II trial: 35% responses(including CRs), duration 12 months, with associated clinical benefit shows remarkable responses in patients with advanced disease unresponsive to known therapies

Bortezomib: From Bench to Bedside

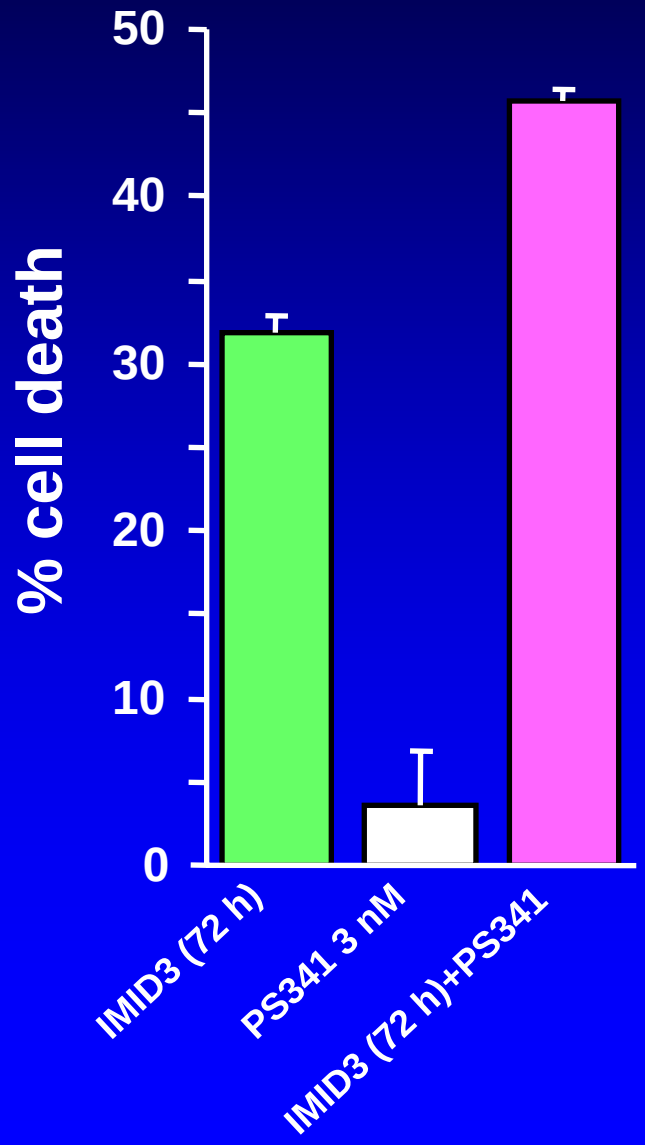
2003 Accelerated approval for relapsed refractory disease by FDA

2003 Phase III trial fully accrued and stopped early due to delay in TTP in Bortezomib cohort

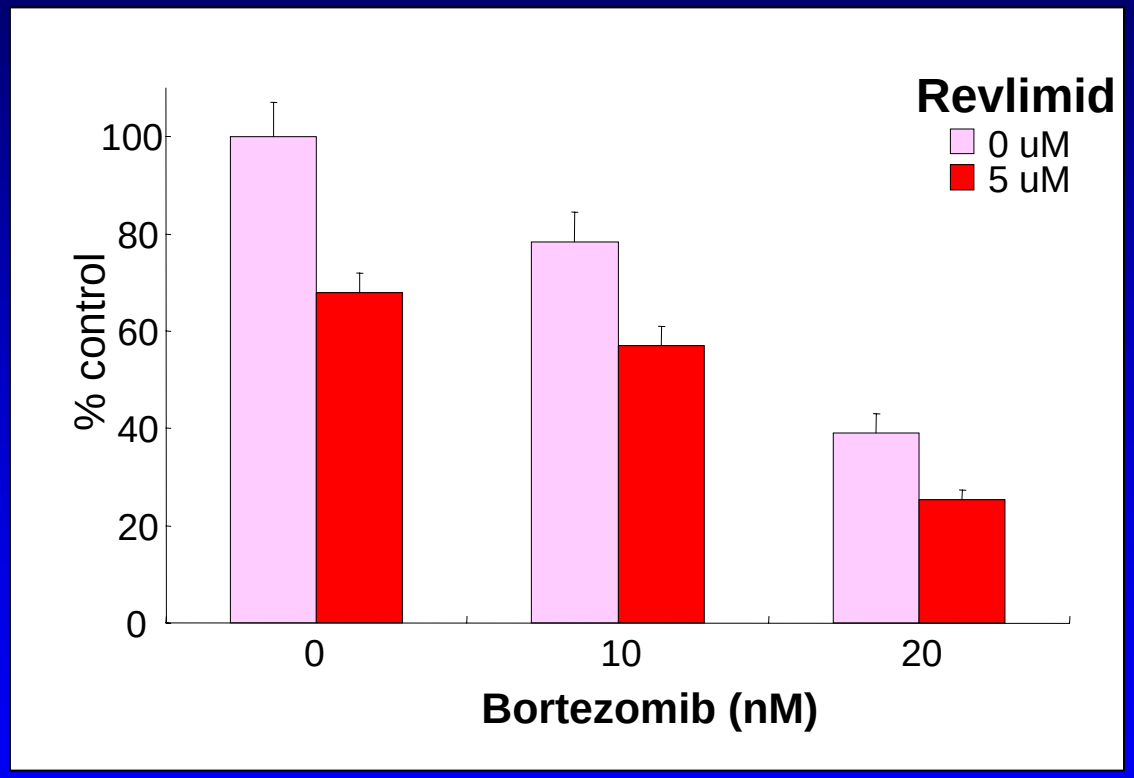
2004 Phase II trials upfront and in combination

2005 FDA approval extended to relapsed myeloma

Combination of Bortezomib +Revlimid



Patient Cells



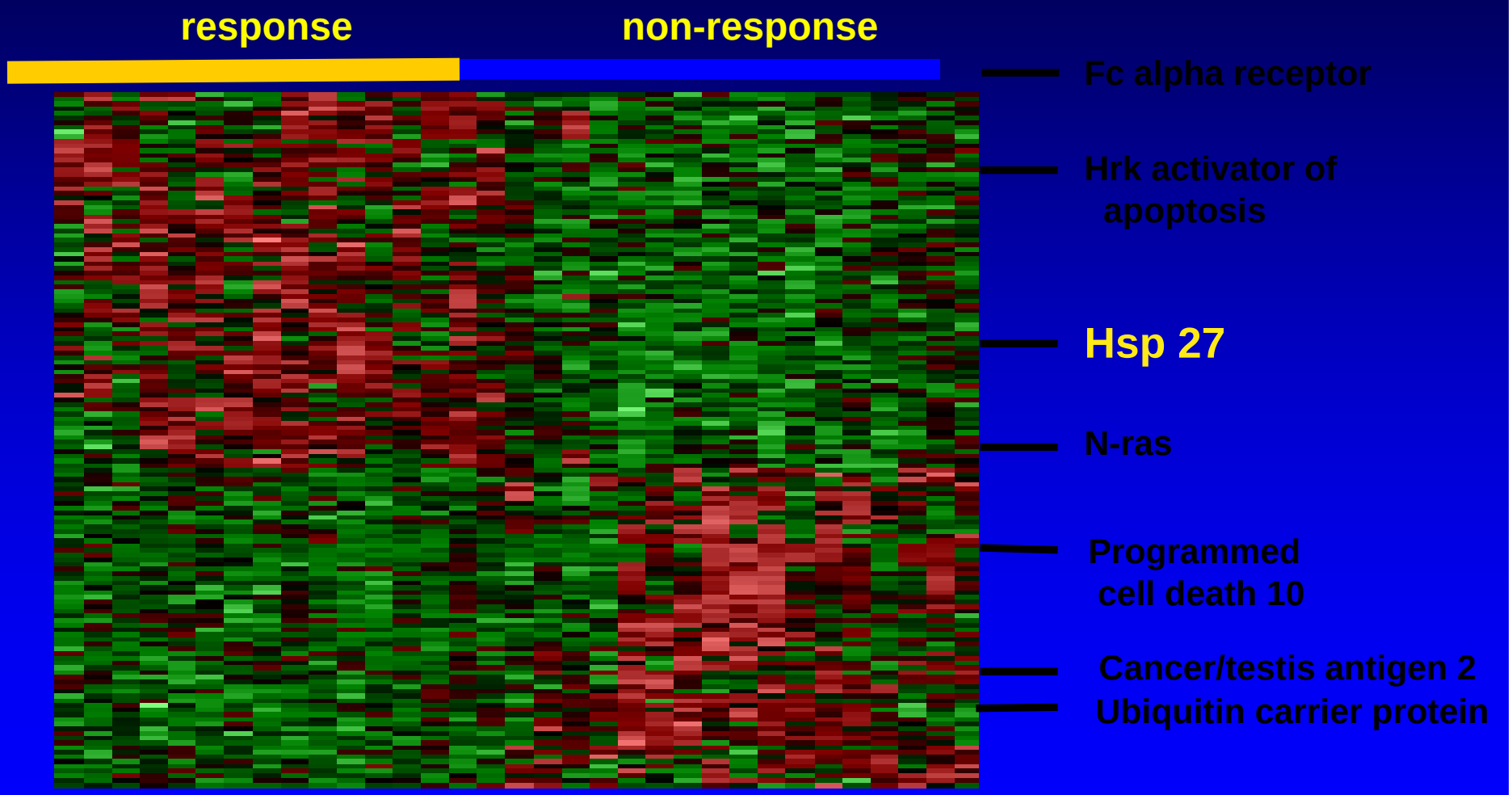
Response (n= 11*)

Cohort	Regimen	No. of Cycles	Response
1	Bortezomib 1.0 mg/m^2 + lenalidomide 5 mg	8–10	PR: 1 of 3 MR: 2 of 3
2	Bortezomib 1.3 mg/m^2 + lenalidomide 5 mg	7–8	CR: 1 of 3 PR: 2 of 3
3	Bortezomib 1.0 mg/m^2 + lenalidomide 10 mg	5–6 2	PR: 2 of 3 PR: 1 of 3
4	Bortezomib 1.3 mg/m^2 + lenalidomide 10 mg	2	PR: 1 of 2 PD**: 1 of 2

*Evaluable **Dex added

RR (CR + PR + MR) : 91%

Gene Microarray Predicts Clinical Response to Proteasome Inhibitor



p38 MAPK Inhibitor (SCIO-469) Enhances PS-341-Induced Cytotoxicity

p38 MAPK ⊣ **SCIO-469**

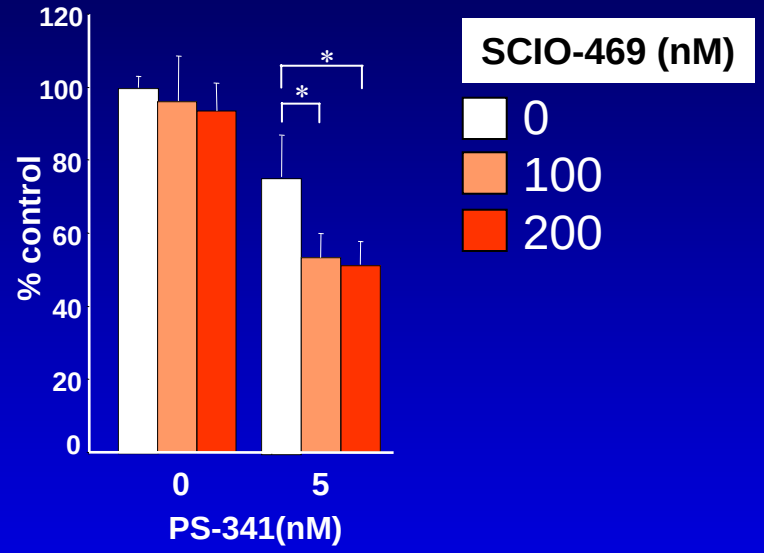
↓

MAP kinase-activated protein kinase-2 (MAPKAPK-2)

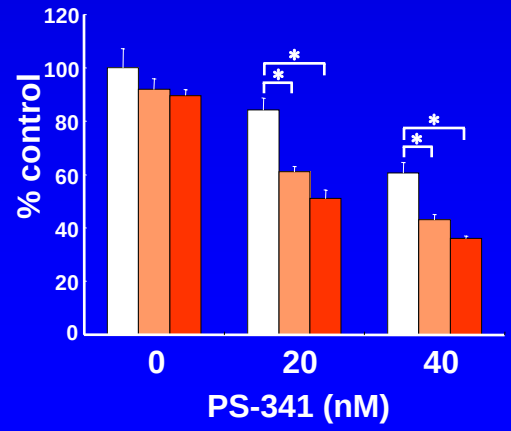
↓

Hsp27

MM.1S



Pat cells (PS-341 resistant)



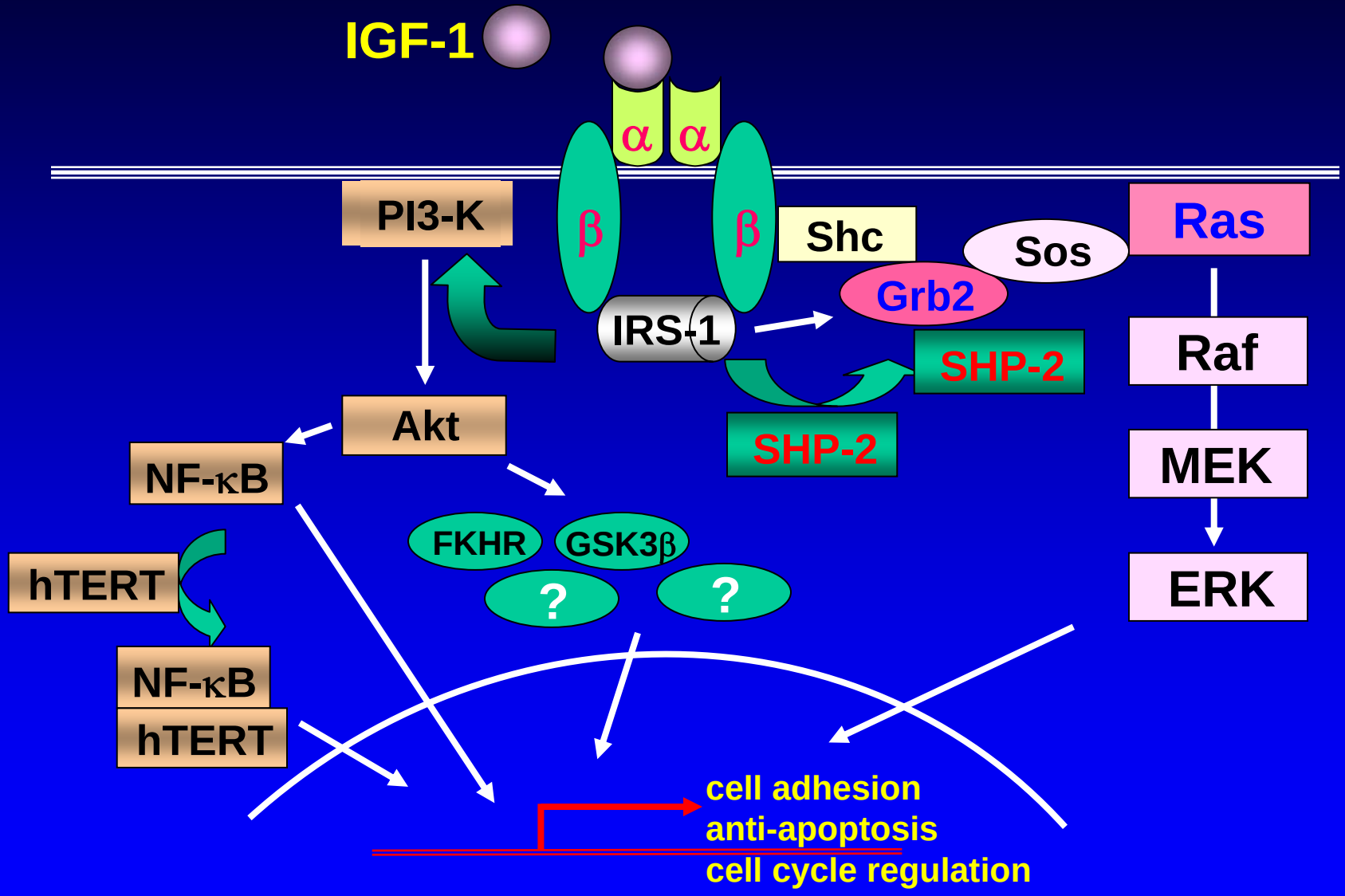
Hideshima et al, Oncogene 2004; in press

IGF Gene Variation and Risk of Multiple Myeloma
SPORE Career Development Award

Birmann BM, Colditz GA, Anderson KC

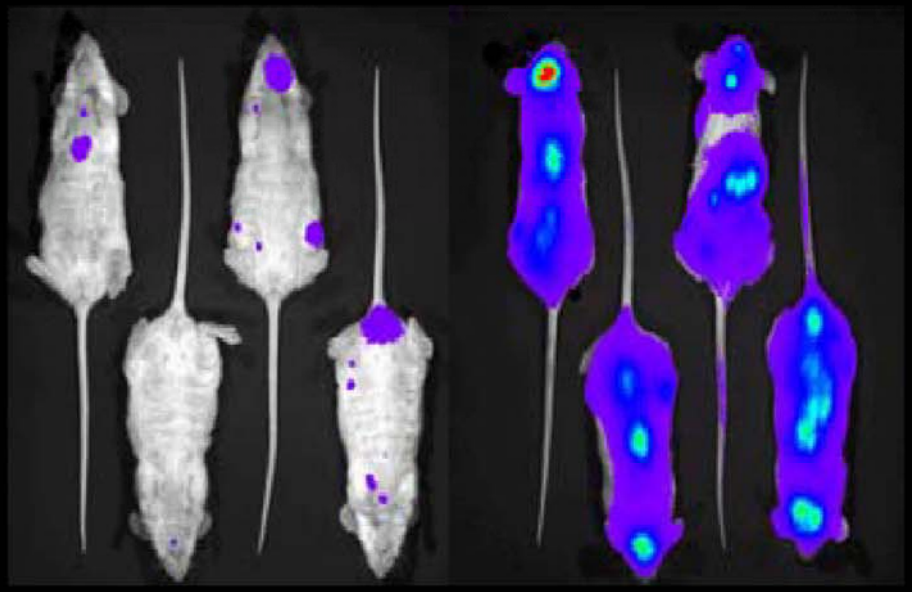
Harvard School of Public Health, Department of Epidemiology
Channing Laboratory, Brigham and Women's Hospital
Department of Medicine, Harvard Medical School
Jerome Lipper Multiple Myeloma Center,
Dana-Farber Cancer Institute
Multiple Myeloma SPORE, Dana-Farber/Harvard Cancer Center

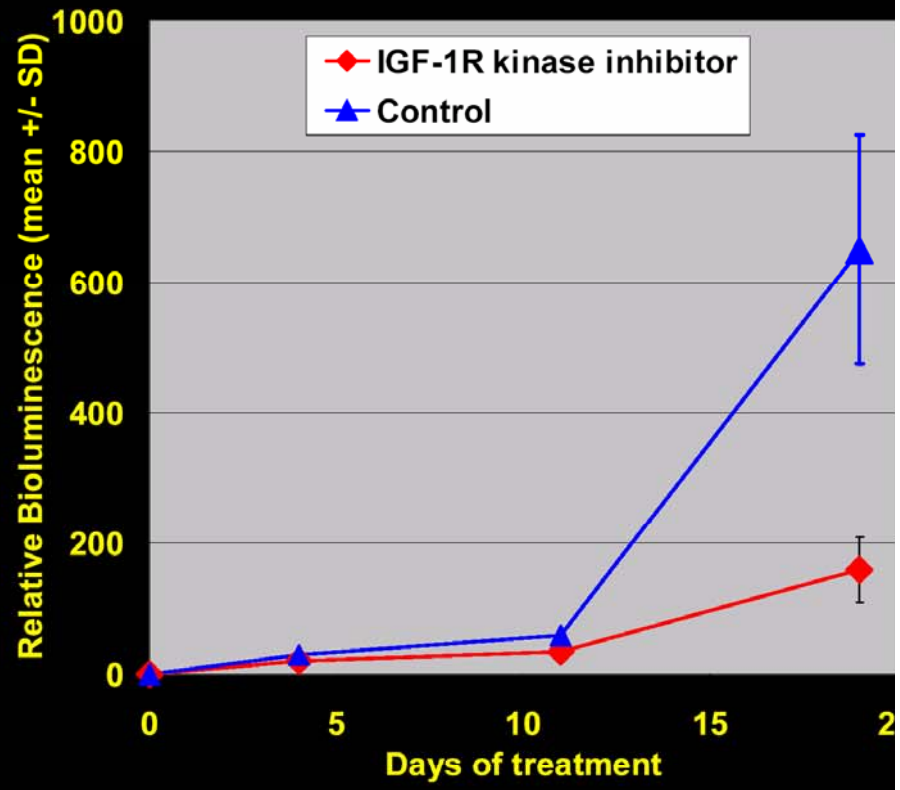
IGF-1Mediated Signaling Cascades in MM



Mitsiades C et al. Oncogene 2002; 21: 5673-83

Anti-MM activity of IGF-1R inhibition in a SCID/NOD mouse model of diffuse MM lesions





Mitsiades C et al, Cancer Cell 2004;221-230

Rationale

- Well accepted that IGF-1 pathway is important in MM pathogenesis
- Lack of epidemiologic data on IGF-1-related risk factors for MM
- IGF pathway implicated in etiology of other malignancies

Nested Case-Control Study

- Two large prospective cohorts based at Harvard University/Channing Laboratory
  - Nurses' Health Study
  - Health Professionals' Follow-up Study
- All incident cases identified through 2002
  - Confirmed self-reported diagnoses
  - DNA available (archived blood or buccal samples)
  - 2 matched controls per case
- At least 55 cases, 110 controls

Genetic Risk Factors for Multiple Myeloma

Dana Farber/Harvard Cancer Center SPORE in Myeloma

Developmental Research Project

Wendy Cozen, Mulugeta Gebregziabher, David Conti, David Vandenberg, Chris Haiman

University of Southern California, Department of Preventive Medicine

Background

- Evidence for genetic risk factors for multiple myeloma:
  - 2-3 fold higher incidence in African-Americans compared to non-Spanish surnamed whites, 4-fold higher incidence compared to Asians
  - Increased risk of multiple myeloma among family members

- What genes?
  - Cytokine genes (ex. IL-1β, IL-4, IL-10, TNF-α)
  - DNA Repair genes (ex. XRCC1-4, RAG-1, Chek 1,2)
  - Growth Factors (ex. IGF-1, Veg-A, Stroma-derived factor 1)

Objectives/Methods

- To evaluate the effect of SNPs of 105 cytokine and DNA repair genes on the risk of multiple myeloma in a multi-ethnic case-control study conducted in Los Angeles.

Subjects:

- Cases are 150 patients with multiple myeloma ascertained from a population-based cancer registry
- Two control groups for comparison
  1) relatives of cases (siblings and cousins, n =112)
  2) population controls from RDD and Medicare (n =131)

Methods, continued

- Laboratory
  - DNA already extracted
  - Genotyping to be performed using Illumina system
  - Will focus on both known functional SNPs and other tag SNPs to test for association of common variants in regions of unknown functional significance
  - Power to detect an Odds Ratio of 1.6 (or 0.6) for allele frequency of $\geq$ 30%

Summary

This study will provide:

- Potential to identify genes relevant to multiple myeloma risk for further targeted studies
- Information useful for construction of haplotypes for cytokine genes
- Two comparisons (relatives, population controls) to enhance validity of findings

Lessons from Rare Cancers

1. A new treatment paradigm targeting both the tumor cell and its microenvironment can overcome drug resistance in myeloma, which serves as a model for other malignancies.

2. Ongoing SPORE collaborative oncogenomic and population studies are identifying novel therapeutic targets governing tumor cell and host interactions, as well as informing the design of clinical protocols.


RON BURTON
HUMILITY